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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 10/509,627
Filing Date: April 29, 2005
Appellant(s): WINGARD ET AL.

Paul M. Rivard
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed 01/12/2010 appealing from the Office action mailed 06/10/2009.

(1) Real Party in Interest

A statement identifying the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

The examiner is not aware of any related appeals, interferences, or judicial proceedings which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

(3) Status of Claims

The following is a list of claims that are rejected and pending in the application:

Claims 12-19 and 36-39 are pending. Claims 14-19 are withdrawn. Claims 12, 13 and 36-39 are rejected under § USC 103(a).

(4) Status of Amendments After Final

The examiner has no comment on the appellant's statement of the status of amendments after final rejection contained in the brief.

(5) Summary of Claimed Subject Matter

The examiner has no comment on the summary of claimed subject matter contained in the brief.

(6) Grounds of Rejection to be Reviewed on Appeal

The examiner has no comment on the appellant's statement of the grounds of rejection to be reviewed on appeal. Every ground of rejection set forth in the Office action from which the appeal is taken (as modified by any advisory actions) is being maintained by the examiner except for the grounds of rejection (if any) listed under the subheading "WITHDRAWN REJECTIONS." New grounds of rejection (if any) are provided under the subheading "NEW GROUNDS OF REJECTION."

The examiner has no comment on the appellant's statement of the grounds of rejection to be reviewed on appeal. Every ground of rejection set forth in the Office action from which the appeal is taken (as modified by any advisory actions) is being maintained by the examiner except for the grounds of rejection (if any) listed under the subheading "WITHDRAWN REJECTIONS." New grounds of rejection (if any) are provided under the subheading "NEW GROUNDS OF REJECTION."

(7) Claims Appendix

The examiner has no comment on the copy of the appealed claims contained in the Appendix to the appellant's brief.

(8) Evidence Relied Upon

6,204,257 Stella 3-2001

Lowrie et al., "The Pediatric Sedation Unit: A Mechanism for Pediatric Sedation", Pediatrics, vol. 102, no. 3, (Sept. 1998), pp. 1-9

(9) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

Claims 12, 13 and 36 are rejected under 35 U.S.C. 103(a) as being unpatentable over Stella et al. (U.S.) in view of Lowrie et al. (Pediatrics, 1998)

Stella et al. teaches a method for the induction or maintenance of general anesthesia by administering compounds of formula I, propofol prodrugs, according to procedures for induction or maintenance of general anesthesia and that the administration is preferably parenterally at the dosage in the range of 0.5 to 10 mg/kg (column 9, lines 1-32). Stella teaches that one skilled in the art of anesthesia will be able to ascertain, without undue experimentation, an appropriate treatment protocol for administering the compound (column 9, lines 13-18). Stella et al. also teaches that prodrugs of propofol, such as those of formula I, are cleaved *in vivo* to generate the parent drug, propofol (column 8, lines 25-40, page 9, lines 1-11).

Stella et al. does not explicitly teach a bolus injection of the claimed compound to produce a sedated state or the amounts of compound in the bolus injection.

Lowrie et al. teaches that the standard for patient sedation for the Pediatric

Sedation Unit is to give propofol intravenously, first as a slow bolus of 1-2 mg/kg, and then continuous infusion (page 5, 1st column, 1st paragraph).

At the time of the invention, it would have been obvious to one skilled in the art to modify the method of Stella et al. and administer a bolus injection of 1-2 mg/kg of the compound of formula I to produce a sedated state, since the compound would generate propofol *in vivo* and propofol in those amounts has been used to produce a sedated state in children. Sedation is a form of anesthesia that ranges from conscious sedation to a deep sedated state. The compound would be reasonably expected to be used for adults and the physiological differences between adults and children would necessitate the need for different dosages. Therefore, it also would have been obvious to optimize the amounts of compound in the bolus injection to produce the desired level of sedation and to account for the compound being used to sedate adults.

(10) Response to Argument

Appellants argue that as in *United States v. Adams*, 383 U.S. 39 (1966), claim 12 is non-obvious at least because persons skilled in the art would not have had a reasonable expectation of success that administering a compound of Formula I in at least one parenteral bolus injection in an amount of from about 2 mg/kg to less than 15 mg/kg, would be effective for producing a conscious sedated state in a human subject.

Stella discloses the prodrug of fospropofol and its administration through different routes and in different doses, i.e. doses of 0.5 mg/kg to 10 mg/kg and 2 µg/kg/min to 800 µg/kg/min. Lowrie describes administering bolus injection of propofol parenterally, but does not describe fospropofol, and does not describe a bolus injection of about 2 mg/kg to less than 15 mg/kg as recited in claim 12. The Examiner has not provided a rationale explaining the reason why a skilled artisan would administer the prodrug in a bolus form in the recited dose. Nothing in Stella indicates a preference for administration via bolus or rapid infusion over longer infusion. Because propofol is produced directly from the prodrug by the action of alkaline phosphatase, and further because propofol was known to cause problems such as cardiorespiratory depression from bolus dosing, one of skill in the art would not have been led to administer the prodrug as a bolus. Propofol is administered to humans as a continuous infusion precisely to avoid these side effects. Thus, because one of ordinary skill would not administer elevated amounts of propofol to humans in a bolus, one of ordinary skill likewise would not have administered elevated amounts of the prodrug to a human in a bolus. The cited art contains no teaching or suggestion that the prodrug could or should be parenterally administered as a bolus in doses higher than those taught in Lowrie.

The Examiner disagrees.

As discussed *supra*, Stella teaches that one skilled in the art of anesthesia will be able to ascertain, without undue experimentation, an appropriate treatment protocol for administering the compound. Further Stella teaches the dosage, mode and schedule of administration of compounds of this invention are not particularly restricted (column 9,

lines 18-20). Since Lowrie teaches the amounts of propofol used in bolus administration to children, it would have been within the purview of the skilled artisan to determine the rates of absorption and the concentration profile of both propofol and fospropofol, which are art recognized steps in the development of any drug for commercial use; and to then determine the amount of fospropofol that would correspond to the propofol which is released into the blood of children. Bolus administration of those amounts taking into account modifications that would be required for treating any patient population that is older than a child would reasonably be expected to produce anesthesia, i.e. sedation ranging from a conscious sedated state to a deeply sedated state, and would involve mere optimization. Further, as cited by Appellant *supra*, Stella et al. teach that substantially the same prodrug of propofol in substantially the same amounts, i.e. 0.5 mg/kg to 10 mg/kg versus 2 mg/kg to less than 15 mg/kg of the instant invention, is administered parenterally. The inclusion of the range of 2 µg/kg/min to 800 µg/kg/min cited by Appellant *supra* would seem to indicate that slow infusions, i.e. of 2 µg/kg/min to 800 µg/kg/min, are one possible mode of administration; and since no time is given for delivering the parenteral injection, i.e. 0.5 mg/kg to 10 mg/kg, it is reasonable that a parenteral bolus injection is within the scope of Stella. It would have been reasonably expected that these amounts of prodrug could be delivered in a bolus parenteral injection; especially with the knowledge of the disclosure of Lowrie that propofol is delivered in a bolus injection for producing sedation in children.

Appellant argues the skilled artisan could not have predicted the differences in the propofol concentration profiles that would result from administration of propofol emulsion versus propofol prodrug; or could not have predicted methods for achieving conscious sedation based on the prior art data.

The Examiner disagrees.

One of skill in the art would not have to be able to predict the differenced in the concentration profiles or methods of achieving conscious sedation. As discussed *supra*, determining the concentration profiles would be within the purview of one of skill in the art. As cited *supra*, sedation is a form of anesthesia that ranges from conscious sedation to a deep sedated state. This teaching combined with the teaching of Stella that one skilled in the art of anesthesia will be able to ascertain, without undue experimentation, an appropriate treatment protocol for administering the compound, would allow one of ordinary skill to be able to ascertain methods of achieving sedation ranging from conscious sedation to a deep sedated state with undue experimentation.

Appellant argues that in the Declaration, dated 03/16/2009, Dr. Shah discusses pharmacology studies that found significant differences in plasma-concentration time profile between propofol and the fospropofol prodrug. Because of these differences, methods of administering fospropofol disodium for achieving conscious sedation could not have been predicted from the data based on propofol. This is supported by Declaration figures 6, 7 and 11. Figure 6 shows that propofol concentration in the plasma from fospropofol had a lower maximum propofol concentration than that from

propofol emulsion injection and that the maximum occurred at a later time. Figure 7, shows that the subjects receiving propofol experienced deeper sedation than those receiving fospropofol, that recovery from fospropofol-induced sedation was more gradual than from propofol injection, and that fospropofol provides a more sustained effect. Figure 11 shows that fospropofol produces a slower maximal effect and a more gradual recovery. The Final office action dated 06/10/2009, dismisses the higher maximum obtained by propofol as expected based on metabolism of fospropofol. But this is mere speculation. No support is supplied to explain the assertion that fospropofol might undergo additional modifications.

The Examiner disagrees.

The studies carried out by Dr. Shah for the Declaration are not novel methods. As cited *supra*, determining the concentration profiles of the drugs is routine and art recognized. One of ordinary skill would not be required to predict methods for achieving conscious sedation. The administration methods could be developed from through art recognized methods. Stella teaches that fospropofol was converted in-vivo to propofol via phosphatase; and the production of propofol was delayed (column 35, line 47-52, column 36, lines 1-5 and Figure 1). Further, one of ordinary skill would readily be aware of the clearance of propofol from the body, and would reasonably assume that some fospropofol is also cleared from the body before conversion. Accordingly, one would reasonably expect that the maximum concentration of propofol derived from the fospropofol would be less than from propofol, since both the parent and the prodrug are cleared from the body, and that the maximum concentration would occur at a latter time.

Since the plasma concentration of propofol from the fospropofol is lower, it would reasonably be expected that the degree of sedation produced by propofol derived from fospropofol would not be as deep as that for propofol; and the sedation would reasonably be expected to wear off at a longer time, since fospropofol produces a maximum, yet lower, concentration at a later time than that of propofol.

Appellant argues that the Diprivan^{R} insert, establishes that one of ordinary skill in the art would have been taught away from administering fospropofol as a bolus because propofol, should not be administered bolus. The Examiner's dismissal of this teaching as based on propofol rather than the claimed compound misses the point. One of ordinary skill in the art would have recognized that propofol is derived from fospropofol and would therefore have been concerned that fospropofol administration would result in potentially dangerous consequences.

The Examiner disagrees.

As discussed *supra*, development of concentration profiles of the two drugs would have been within the purview of the skill artisan, and would be art recognized as integral steps in drug development. Based on the profiles and other attainable data, one of ordinary skill would have been aware of the differences in the plasma concentrations of propofol produced by both drugs. Accordingly, the product insert may have taught away from administering propofol bolus, but would not teach anything about bolus fospropofol since it is a distinct drug with a distinct plasma concentration profile

than that of propofol; especially when taking into account the teaching of Lowrie cited *supra*, that propofol has been successfully administered bolus to children.

Appellant argues that no reasoning has been provided to support the assertion that a teaching 5 mg/kg and 10 mg/kg are effective does not support effectiveness of amounts between 2 mg/kg to less than 15 mg/kg. No reasoning has been provided for the assertion that administering a compound as an alkali salt is not the same as administering a compound in its salt form. The salt moiety is part of the group that is cleaved from the prodrug and releases the active drug; therefore differences in salt types are unlikely. Claim 37, requires an alkali metal salt and claim 39 requires a sodium salt, which renders the distinction between acid and alkali metal salt moot.

The Examiner disagrees.

Appellant argued alleged surprising and unexpected results were demonstrated in the Examples of the Application. The Examiner's response which is presented in this section was in response to the specific prodrug form used and the specific amounts of prodrug used in the Examples. In the Examples, the Appellant has demonstrated that a bolus does of 5 mg/kg and 10 mg/kg of the disodium salt of the prodrug of formula I produces conscious sedation. The amounts are not commensurate with the scope of claim 12, which recites an amount of 2 mg/kg to less than 15 mg/kg. There is no data concerning the production of conscious sedation by bolus administration of the prodrug in amounts from 2 mg/kg to less than 5 mg/kg. Appellant has provided evidence that the prodrug produces lower maximum concentrations of propofol than administration of

propofol, but has not provided any data on the type of sedation, if any, that is produced by administration of the prodrug at the lower end of the concentration range of instant claim 12. Similarly there is no data provided concerning the production of conscious sedation by bolus administration of the prodrug in amounts from 10 mg/kg to any other amount which is greater than 10 mg/kg but less than 15 mg/kg. Appellant has put forward arguments concerning "potentially dangerous consequences" that would be expected by one of skill in the art of delivering the prodrug at the higher concentrations of the instant method, but has not provided any data on the higher end of the concentration range of instant claim 12. Accordingly, claim 12 is broader in scope than the actual showings from the Examples. Appellant provided no data in the Examples on the production of conscious sedation by the acid form of the prodrug or any other salt other than sodium. Even assuming *arguendo* that the claims, i.e. an acid form or alkali metal salt form, are commensurate in scope with the showings of the Examples, Stella teaches the acid form and metal salt forms of substantially the same prodrug as the instant compound (column 5, lines 59-62 and column 9, lines 1-15).

Appellant argues that claims 13, 37 and 39 require dosages of about 5 mg/kg to 10 mg/kg which distinguishes the cited references and makes moot the contention regarding the broader dosage range. In the Declaration, Dr. Shah concludes that methods of administering fospropofol disodium for achieving conscious sedation could not have been predicted form data based on propofol.

The Examiner disagrees.

As discussed *supra*, Stella teaches substantially the same prodrug of propofol in amounts, i.e. 0.5 mg/kg to 10 mg/kg, which overlaps the dosage range of claims 13, 37 and 39; and that the prodrug is administered parenterally to produce anesthesia, i.e. sedation ranging from conscious sedation to a deep sedated state. The response to the Declaration and being able to make predictions based on the data of propofol has been presented *supra*.

Appellant argues that claims 36 and 38 specify a narrower dosage range of about 5 mg/kg to about 7.5 mg/kg, there is nothing in Stella or Lowrie that would have led the skilled worker to this particular dosage range of a bolus injection. The only basis for reaching such a conclusion is the hindsight gleaned from reading the present specification.

The Examiner disagrees.

As discussed supra, the dosages of the instant claims 36 and 38 overlap those disclosed by Stella. Further, motivation for development of the mode of administration to produce anesthesia, i.e. sedation ranging from conscious sedation to a deep sedated state through art recognized practices, such as the bolus administration of Lowrie, and optimization, is discussed *supra*.

(11) Related Proceeding(s) Appendix

No decision rendered by a court or the Board is identified by the examiner in the Related Appeals and Interferences section of this examiner's answer.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

/Darryl C Sutton/

Examiner, Art Unit 1612

Conferees:

/Frederick Krass/

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